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Preconditioning, Collateral Recruitment and Adenosine

We read with interest the recent article by Billinger et al. (1). It shows that the myocardial adaptation to repetitive ischemia during percutaneous transluminal coronary angioplasty (PTCA) is partially due to collateral recruitment, which accounted for 30% of the observed variation in intracoronary ST segment shifts and is mainly related to ischemic preconditioning. These findings are in agreement with several previous reports by our group (2-4) and others (5,6) using the PTCA model of ischemic preconditioning. However, it is surprising that, by contrast to extensive evidence supporting a prominent role for adenosine and its receptors in mediating the cardioprotective effects of preconditioning in both experimental (7-9) and clinical (10-12) studies, Billinger et al. (1) failed to show pharmacologic preconditioning with adenosine during PTCA. However, the authors measured ST segment shifts only 1 min after the beginning of balloon inflation, a period insufficient for the achievement of the full evolution of ST segment shift, as previously demonstrated (6). Furthermore, for the assessment of myocardial ischemia severity, Billinger et al. (1) adjusted ST segment amplitude with QRS amplitude. This adjusted index of myocardial ischemia remains to be validated in the experimental setting of repeated balloon inflations, especially because during PTCA there are changes in the QRS amplitude, which are variably correlated ($r^2 = 0.29$ to 0.81) with those of ST segment shifts (13). Surprisingly, unadjusted ST segment changes, which have been experimentally validated (14,15), are not provided. Thus, it would be interesting to know whether the results obtained by Billinger et al. (1) regarding the effects of adenosine on preconditioning are confirmed when absolute ST segment changes measured after 2 min of balloon inflation are utilized. Similar considerations apply to the relation between changes of ST segment shift and those of collateral flow index. This would make it possible to compare their results with those of several previous published studies on this topic (2-6,10-12,16).

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REPLY

We thank Tomai and colleagues for their comments on our recent investigation (1). Their reading of our report is different from the wording as well as from the intended meaning, which was that even in patients with only a few collateral channels, their recruitment, as an adaptive mechanism to repetitive ischemia does occur. Our study did not show that the development of ischemic tolerance "is mainly related to ischemic preconditioning." If collateral recruitment was observed to account for 30% of the variation in electrocardiographic ST segment shifts, the quoted conclusion certainly cannot be drawn. It can only be suggested (as we did in our conclusion) that ischemic preconditioning may be a relevant factor in the development of tolerance to ischemia. It is correct that we could not reproduce recent data from the published reports on the effectiveness of adenosine as "preconditioner." This was the case despite the fact that we used a study protocol and dosage of adenosine identical to that used by Leesar et al. in their investigation (2). To call the three cited studies in humans on the effect of adenosine "extensive evidence" appears slightly exaggerated to us.